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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,423	09/19/2003	Blas Frangione	05986/100K433-US2	8605

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
10/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,423	FRANGIONE ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/22/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/22/2007 has been entered.

2. Claims 1-9 and 16-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 10-15 and 21-23 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 103

4. Claims 10-15, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6866849 ('849) (of record), in view of Ghanta *et al.*, 1996, J. Biol. Chem. 271(47):29525-29528 (of record), US Patent 6962707 ('707) (of record), Maillere *et al.*, 1995, Molecular Immunology 32(17/18): 1377-1385 (of record), Yankner *et al.*, Science, Vol. 250, No. 4978. (Oct. 12, 1990), pp. 279-282; Solomon et al., PNAS 1997 94: 4109-4112; and Pike *et al.*, Journal of Neurosci. 1993 Apr;13(4):1676-87. Although this is a new rejection with additional references not previously relied upon, the basis for the rejection is retained from the rejection of record. In that regard, Applicant's arguments filed 08/22/2007 have been fully considered but

they are not persuasive. Claims 10-15 and 23 are drawn to an isolated peptide comprising the amino acid sequence of SEQ ID NO:1, which consists of the N-terminal 30 amino acids of human amyloid β (Aβ), with modifications comprising addition of 4-10 lysine or aspartate residues at either end or (in claims 13 and 14) amidation of the C-terminus. Claims 21 and 22 are drawn to a method for inducing an immune response comprising administering said peptide. Applicant generally argues that the prior art does not teach or suggest the synthetic Aβ peptides defined by the instant claims.

5. First, it is not necessary that the prior art teach or suggest the precise synthetic Aβ peptides defined by the instant claims. The rejection holds that the recited peptides are obvious to one of skill in the art because they are the result of combining of known elements by known methods to yield predictable results.

6. The '849 patent teaches (throughout) administration of a peptide consisting of the first 39 amino acids of Aβ (Aβ1-39) for the purpose of evoking a therapeutic antibody response (see claim 36). As Aβ1-39 *comprises* amino acids 1-30, this peptide meets the sequence limitation of instant claim 10, where n is 1. The '707 patent teaches the benefit of immunization with N-terminal peptides of Aβ as small as the first 12 amino acids (see Fig. 13 of the '707 patent) and further teaches immunization with multimers (*i.e.* n= 2 or more as in instant claim 23; see claim 6 of the '707 patent). Fig. 13 of the '707 patent also shows that high antibody titers were obtained after immunization with Aβ13-28 but much lower titers were obtained with Aβ25-35 or Aβ33-42. It is evident, therefore, that immunogenic sequences are found within amino acids 1-12 and 13-28 of Aβ, and that the amino acids from about 25-28 to 42 are not highly

immunogenic. Therefore, it is predictable that any peptide that comprises all of the first 28 amino acids of Aβ, such as the Aβ1-30 of the instant claims, should evoke production of antibodies. Indeed, antibodies raised against Aβ1-28 cause disaggregation of Aβ fibrils and inhibit the neurotoxicity of Aβ (Solomon et al., PNAS 1997 94: 4109-4112, see Abstract).

7. It is further predictable that that Aβ1-30 would have the asserted advantage of lowered risk of toxicity to humans. It is well known in the art that forms of Aβ that comprise nearly all of the naturally occurring Aβ1-42 are neurotoxic. For example, Yankner *et al.* reported a high toxic activity for Aβ1-38 and Aβ1-40 (Table 1). Ghanta *et al.* used Aβ1-39 used as the positive control for Aβ toxicity in their studies aimed at identifying inhibitors of toxicity (see Figures 3 and 5). Therefore, one of skill in the art would recognize that a disadvantage to immunizing with Aβ1-39, as taught in the '849 patent, would be that the immunogen is itself neurotoxic. It is also well known that toxicity is greatly diminished by omission of amino acids from the C-terminus of Aβ. Pike *et al.*, for example, reported that Aβ1-28, **Aβ1-30**, and Aβ1-33 each show little toxicity to neurons in culture (see Figure 4). Similarly, Yankner *et al.* showed that Aβ1-28 appeared to be completely nontoxic to hippocampal neurons when compared at an equal concentration to Aβ1-40 (Table 1). Note also that Aβ1-28 displayed toxicity at higher doses (Yankner *et al.*, Table 1). Thus, although the toxicity of Aβ1-28 is greatly reduced relative to Aβ1-40, the potential for toxicity remains, which would still be a concern for *in vivo* administration.

8. The prior art further teaches the modifications recited in the instant claims will have the asserted advantages of stimulating the immune response and reducing toxicity. The '707 patent teaches a polylysine or polyglutamic acid linked to the amino or carboxyl terminus of an

immunogenic Aβ peptide (see claim 11). Polylysine and polyglutamic acid are identified as immunostimulatory molecules (column 15, lines 61-62). Therefore, the '707 patent teaches that addition of polyamino acids to an Aβ peptide immunogen is advantageous, but does not teach polyaspartate or the 4-10 amino acid limit. The substitution of aspartate for glutamate is conservative, as both are acidic amino acids.

9. Ghanta *et al.*, citing earlier work, teach that the toxicity of Aβ is inhibited in Aβ aggregates that incorporate Aβ peptides that are covalently modified by addition of an element that disrupts β-sheet formation (see abstract). Ghanta *et al.*, further identify lysine hexamers as effective disrupting elements (p. 29525, 1st paragraph under "Experimental Procedures" and figures 1, 3-5). Ghanta *et al.* demonstrated the effects of lysine hexamers linked to Aβ15-25 (p. 29525, 1st paragraph under "Experimental Procedures"), which comprises amino acids critical for aggregation. Thus, Applicants argue (Response, page 9) that the peptides described in Ghanta are strictly inhibitors that bind to Aβ15-25 and not immunogens as in the instant claims. Actually, Ghanta and one of skill in the art seeking to use Aβ peptides as immunogens are concerned with the common problem of reducing toxicity. Binding of Aβ to Aβ is the first step in aggregation which leads to toxicity and the amino acids of Aβ15-25 are retained within Aβ1-30. Therefore, it is predictable that lysine hexamers taught by Ghanta would be effective in inhibiting the toxicity of Aβ1-30.

10. Maillere *et al.*, teach that C-terminal amidation decreases proteolytic degradation of peptides and enhances the capacity of the peptide to activate lymphocytes (see abstract). To further emphasize the point, consider the following excerpts of the Maillere abstract: "Acetylation at the N-terminus as well as amidation at the C-terminus enhanced the capacity of

the peptide to activate T cells...Together, our data indicate that (i) the T cell stimulating capacity of a peptide is associated with its lifespans in the free and MHC II bound states; and (ii) these lifespans can be greatly enhanced by introducing fine chemical modifications at N- and C-termini. These data may have some implications in designing more potent peptidic immunomodulators." Following Maillere's strong suggestion, the skilled artisan seeking to evoke an immune response to Aβ peptides would expect that C-terminal amidation, as recited in instant claims 13 and 14, would be an advantageous modification.

11. The instant specification provides no evidence that the claimed combination of elements, Aβ1-30 modified by polyamino acids and/or C-terminal amidation, performs any differently than would be predicted by the teachings of the prior art with respect to each element. Therefore, the combined teaching of the recited references renders the inventions of claims 10-15, and 21-23 prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
26 October 2007

MANJUNATH N. RAO, PH.D.
Supv. PRIMARY EXAMINER
A-V- 1647